ORIGINAL ARTICLE

Bilastine and Quality of Life

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Abstract

The evaluation of quality of life (QoL) and its modification through therapeutic interventions has become a prioritary concern in recent years and a requirement on the part of regulatory agencies for the authorization of new drugs. In clinical studies of allergic disorders, particularly allergic rhinitis and urticaria, different types of generic questionnaires have been used – especially disease specific instruments such as the *Rhinoconjunctivitis Quality of Life Questionnaire* (RQLQ) or skin disease specific tools such as the *Dermatology Life Quality Index* (DLQI). Throughout its clinical development, bilastine has been shown to be more effective than placebo and at least as effective as cetirizine, levocetirizine, fexofenadine or desloratadine in controlling the symptoms of seasonal allergic rhinitis and chronic urticaria. QoL has been studied as a secondary objective in three allergic rhinitis clinical trials, using the RQLQ, in a total of 2335 patients. Likewise, in chronic urticaria, QoL has been evaluated using the DLQI in a total of 525 patients, versus levocetirizine and placebo. The improvement in the QoL parameters in these studies (RQLQ or DLQI domains) at all times proved proportional to the symptoms improvement. In general, the data obtained relating to changes in QoL are concordant with the mean global visual analog scale (VAS in mm) values and their changes, from the beginning until the end of the treatment period, for all of the trials, for bilastine and all its comparators.

Key words: H_1 antihistamines. Bilastine. Quality of life. Visual analog scale. *Rhinoconjunctivitis Quality of Life Questionnaire* (RQLQ). *Dermatology Life Quality Index* (DLQI). Allergic rhinitis. Chronic urticaria.

Resumen

La valoración de la calidad de vida (CdV) y de su modificación por medio de intervenciones terapéuticas se ha convertido en los últimos años en un objetivo primario y en una exigencia de las agencias reguladoras para la aprobación de nuevos medicamentos. En los estudios clínicos de trastornos alérgicos, y en particular de la rinitis alérgica y la urticaria, se han venido empleando distintos tipos de cuestionarios genéricos, y sobre todo instrumentos específicos de enfermedad, como el *Rhinoconjuntivitis Quality of Life Questionnaire* (RQLQ) o específicos de enfermedad cutánea, como el *Dermatology Life Quality Index* (DLQI). A lo largo de todo su desarrollo clínico, bilastina ha demostrado ser un fármaco más efi caz que el placebo y al menos tan efi caz como cetirizina, levocetirizina, fexofenadina o desloratadina en el control de los síntomas de la rinitis alérgica estacional y la urticaria crónica; la variable CdV se ha estudiado como objetivo secundario en tres ensayos clínicos en rinitis alérgica, por medio del instrumento RQLQ, en un total de 2.335 pacientes; asimismo, en urticaria crónica la CdV se ha estudiado por medio del instrumento DLQI en un total de 525 pacientes, frente a levocetirizina y placebo. La mejoría en los parámetros de CdV en estos estudios (dominios RQLQ o DLQI) ha sido en todo momento proporcional a la mejoría sintomática. En general, los datos de cambio en la CdV obtenidos son concordantes con las medias globales de escalas analógicas visuales (EVA) en mm y sus cambios entre el principio y el final del tratamiento para el conjunto de los ensayos con bilastina y todos sus comparadores.

Palabras clave: Antihistamínicos H_1. Bilastina. Calidad de vida. Escala analógica visual. *Rhinoconjuntivitis Quality of Life Questionnaire* (RQLQ). *Dermatology Life Quality Índex* (DLQI). Rinitis alérgica. Urticaria crónica.

Introduction

Health-related quality of life (HRQoL) measures the functional effects of a disease and its treatment from the particular perspective of the patient. HRQoL is therefore a subjective concept which over the last decade has been shown to be of clinical and economical importance – to the point of having become a basic indicator in all chronic illnesses and in assessing the comparative efficacy of different treatments, whether based on drugs or otherwise. HRQoL is particularly important in many allergic disorders, and in particular in allergic rhinitis and urticaria, since these are disorders associated with low mortality but with a high prevalence and strong impact upon the daily life of the patient – thereby generating important economical and social costs. Thus, HRQoL now forms part of the clinical follow-up of these patients, and it is widely used in different scenarios, from clinical trials (where its inclusion is required by the regulatory agencies as part of current legislation) to pharmacoeconomical studies.

The evaluation of HRQoL is particularly important in the development of antihistamines, as these are the most commonly used drugs in application to the most prevalent allergic disorders. We must also consider whether the concept of quality of life is interchangeable between respiratory allergy and chronic urticaria (CU), and whether we can expect the same from a given antihistamine in both diseases. In different studies the correlation between the symptom scores and the scores obtained for the HRQoL questionnaires has been found to be only moderate, both in perennial rhinitis (r=0.59) [1] and in CU (r=0.64-0.69) [2] – this emphasizes the net difference between symptom intensity and subjective perception of the impact of the symptoms in real life. Nevertheless, the few comparisons that have been made in these terms indicate that patients with CU are more affected in their daily life than patients with rhinitis and/or asthma, in relation to aspects such as sleep, eating behaviour, occupational activity and general physical and psychological functioning [3].

Health-related Quality of Life: Concepts and Evaluation in Rhinitis and Urticaria

The classical definition of health-related quality of life (HRQoL) is "the functional effects of a disease and its consequent treatment upon the patient, as personally perceived by the patient" [4]. The instruments used to measure these effects in allergic conditions are the many existing HRQoL questionnaires (Table 1)[5]. As it is known and universally accepted, any HRQoL questionnaire must satisfy some essential psychometric conditions related to *viability* (reasonable length and easy to explain to patients), validity (it measures what is being evaluated, and discriminates severity referred to the symptom scores), reliability (reproducibility and internal consistency, or the absence of contradictions in the responses) and sensitivity to change (capacity to reflect symptom variations after a given treatment) [6] (Table 2).

There are two basic types of HRQoL questionnaires: generic questionnaires, which evaluate general aspects of HRQoL in different populations and are appliable to different diseases and treatment interventions, allowing the comparison of results; and *specific questionnaires*, which detail the important factors associated to a given disease in a specific population. These latter instruments are useful when comparing drugs in one same disease, and offer greater sensitivity and specificity, though they do not allow comparisons between different diseases [5,6].

Both types of questionnaires – generic and specific – have been used in application to allergic disorders. The most widely used generic questionnaire is the SF-36 (*Medical Outcome Study 36-Item Short Form Health Survey*)[7], which has been validated for its application to respiratory allergic disease [8] and is also used to compare the latter versus CU in terms of HRQoL [3]. However, for the study of allergic disorders and of the drugs used to treat them, the most useful questionnaires are the disease-specific or skin disease-specific instruments, which offer greater sensitivity to change and specificity. The

Table 1. HRQoL questionnaires most commonly used in rhinitis and urticaria (Modified from ref. 5, Colás et al.)

Generic indexes *Visual Analogue Scale for Quality of Life (VAS-QoL)* *Feeling Thermometer, Quality of Well-Being, Standard Gamble*
Generic profiles *Medical Outcomes Survey Short Form-36 (SF-36)* *Medical Outcomes Survey Short Form-12 (SF-12)* *Euro-QoL* *Munich Life Dimension List (MLDL)* *Satisfaction Profile (SAT-P)* *Work Productivity and Activity Impairment (WPAI-AS)*
Specific questionnaires in rhinitis *Rhinoconjunctivitis and Rhinitis Quality of Life Questionnaire (RQLQ)* and variants – Mini-RQLQ – RQLQ-children – RQLQ-adolescents – *Nocturnal Rhinitis Quality of Life Questionnaire* (NRQLQ) ESPRINT and mini-ESPRINT questionnaire *Rhinasthma* *Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ)* *Rhinitis Outcome Questionnaire*
Specific instruments used in dermatological disease *Dermatology Life Quality Index (DLQI)* *Children's Dermatology Life Quality Index (CDLQI)* *Dermatology Quality Of Life Scales (DQOLS)* *Dermatology- Specific Quality of Life (DSQL)* *Skindex-29* *Skindex-16* *Questionnaire on Experience with Skin Complaints (QES)* *VQ- Dermato*
Specific instruments used in chronic urticaria *Chronic Urticaria and Quality of Life Questionnaire* (CU-Q2oL)

Table 2. Psychometric characteristics of the HRQoL questionnaires (Modified from ref. 6, Contreras Porta et al)

1. Viability
   Reasonable extent and understandable for the patient
   Viability study:
      Analysis of missing responses
      Ceiling and floor effects
2. Validity
   Measures exactly what is being evaluated
   Validity study:
      Discriminating capacity with respect to severity according to symptoms
      Convergence and divergence with other instruments that measure the same
3. Reliability
   Reproducible and without contradictions in the responses
   Reliability study:
      Internal consistency (Cronbach α coefficient > 0,70)
      Test-retest reliability – Intraclass correlation coefficient 0,7 – 0,9
4. Sensitivity to change
   Capacity to reflect pre- and post-treatment changes
   Study of sensitivity to change:
      Effect size: Mean post - Mean pre/Standard deviation pre-MID or MSD (minimum important or significant clinical difference)

questionnaires considered to be the most useful in clinical trials and epidemiological studies of rhinoconjunctivitis in our setting are the *Rhinoconjunctivitis Quality of Life Questionnaire* (RQLQ) developed by Juniper [9] and validated in its Spanish version [10], and the specific ESPRINT questionnaire [11] and its short forms, the Mini-RQLQ and ESPRINT-15 [12]. In the case of CU, different skin disease-specific questionnaires have been employed, and more recently a specific questionnaire for CU has been developed – the so-called *Chronic Urticaria Quality of Life Questionnaire* (CU-Q2oL) [13], the Spanish version of which has recently been validated by our group [14]. The most widely used questionnaire in most of the clinical trials is the *Dermatology Life Quality Index* (DLQI)[15], which has been shown to be useful in assessing the most prevalent chronic skin conditions, and has also been specifically validated for CU [16].

Visual analog scales (VAS) have been validated as instruments for exploring severity in rhinitis [17], in urticaria [18] and in other allergic diseases, particularly in pediatric patients [19]. In practice, they are regarded as complementary tools in the measurement of HRQoL.

Bilastine and HRQoL in Allergic Rhinitis

Although allergic rhinitis is not a serious illness, it constitutes a global health problem, due to its enormous and increasing prevalence [20]. It is the main reason for consultation in 55.5% of all cases in Spanish allergy clinics [21], and it is known to alter the patients social life, producing alterations in nighttime rest and inducing daytime drowsiness [22], with an adverse impact upon school [23] and work performance [24]. In addition, allergic rhinitis is associated to a number of disorders with a strong global socioeconomic impact such as asthma, rhinosinusitis, otitis media, nasal polyposis, lower respiratory tract infections, obstructive apnoea syndrome, atopic dermatitis or food allergy [25], with the subsequently added impact upon HRQoL.

The ARIA document (*Allergic Rhinitis and its Impact on Asthma*), recently updated and adapted to the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) [26], has generalized a classification of rhinitis based on the duration (intermittent versus persistent) and severity of the symptoms: mild and moderate / severe, depending on the importance of the symptoms and the impact upon daily life as measured by four items or questions (sleep, work/studies, activities, bothersome symptoms). A recent modification of this classification has introduced a new criterion, differentiating among three categories instead of two: mild (no item affected), moderate (1-3 items affected) and severe (all items affected) [27]. Previous epidemiological studies by our group suggest that in our environment, over one-third of all cases of allergic rhinitis in adults [28] and almost 90% of the cases in children [29] are rated as moderate-severe by the patients themselves.

Non-sedative second-generation antihistamines (AHs) that do not interact with the P450 cytochrome enzymatic system remain as the first-choice drugs for the treatment of allergic rhinitis [26]. Antihistamines have also been shown to improve HRQoL when evaluated as a primary objective [30,31]. As it has already been said, correlation between the HRQoL questionnaires and the symptom scores is only moderate, the same as the correlation obtained from the measurement of nonspecific nasal responsiveness [1] - though the correlation is generally positive and proportional to symptom improvement. The studies that compare different antihistamines in terms of efficacy and/or effect upon HRQoL in allergic rhinitis suggest that there are no significant differences among the different substances, and in many clinical trials a strong placebo response is curiously observed – possibly reflecting the natural course of the disease, symptom fluctuations, or biases of some other nature [32].

Bilastine in a single daily dose of 20 mg has been shown to be more effective than placebo and as effective as cetirizine [33], fexofenadine [34] and desloratadine [35] in controlling the symptoms of seasonal allergic rhinitis.

Improvement in the HRQoL parameters, based on the RQLQ questionnaire, was observed as a secondary objective in a total of 2335 patients, in allergic rhinitis clinical trials. The RQLQ comprises 28 items or questions, grouped into 7 domains (limitation of activity, sleep, nasal symptoms, eye symptoms, non-nasal/non-eye symptoms, practical problems, and emotional functioning). There are three "patient specific" questions in the activity domain, allowing the patient to choose those three daily activities that are most affected by rhinoconjunctivitis. The patients recall their discomfort in

the past week as a result of the symptoms, and score each question on a scale of 0-6 (0 = "*has not bothered me at all*", and 6 = "*has bothered me very much*"). The RQLQ score is the mean of the scores of the 28 questions, and means of each domain are also calculated. The minimum significant difference is 0.5 points. On the other hand, all the studies carried out with bilastine estimated and analyzed the VAS scores for discomfort associated to rhinitis.

Bilastine and HRQoL in seasonal allergic rhinitis

When comparing bilastine 20 mg/day versus desloratadine 5 mg/day and placebo in 720 patients randomized to three homogeneous groups over a period of 14 days [35], a significant reduction was observed in the symptom scores in both active drug groups versus placebo (p<0.001) over the entire duration of treatment – with no significant differences in the efficacy profiles between the bilastine and desloratadine groups. Evaluation of HRQoL was carried out based on the RQLQ in a subgroup of 511 patients homogeneously distributed among the three treatment groups. As we can see in Table 3, the RQLQ score on day 14 showed significant differences between placebo and bilastine, and also between placebo and desloratadine, in relation to the total score and for most of the domains considered separately. As expected, the correlation between the changes in the symptom scores and changes in the HRQoL questionnaire was moderate (r=0.59), with no significant differences among the three groups.

Table 3. Bilastine versus desloratadine in seasonal allergic rhinitis. Improvement in the specific RQLQ scores after two weeks of treatment

RQLQ domains	Placebo n=245	Bilastine n=233	Desloratadine n=242	P-value (Kruskal-Wallis)
Activity	-1.5 (1.6)	-2.0 (1.6)	-1.9 (1.6)	p=0.008
Sleep	-1.0 (1.6)	-1.1 (1.5)	-1.3 (1.6)	p=0.020
Non-nose/non-eye symptoms	-1.0 (1.4)	-1.3 (1.3)	-1.3 (1.3)	p=0.020
Practical problems	-1.7 (1.9)	-2.2 (1.8)	-2.1 (1.8)	p=0.023
Nasal symptoms	-1.6 (1.7)	-1.9 (1.6)	-1.9 (1.6)	P=0.095
Eye symptoms	-1.2 (1.6)	-1.6 (1.6)	-1.6 (1.4)	p=0.011
Emotions	-1.1 (1.4)	-1.4 (1.5)	-1.2 (1.3)	p=0.075
Total RQLQ	-1.3 (1.3)	-1.6 (1.2)	-1.6 (1.2)	p=0.005

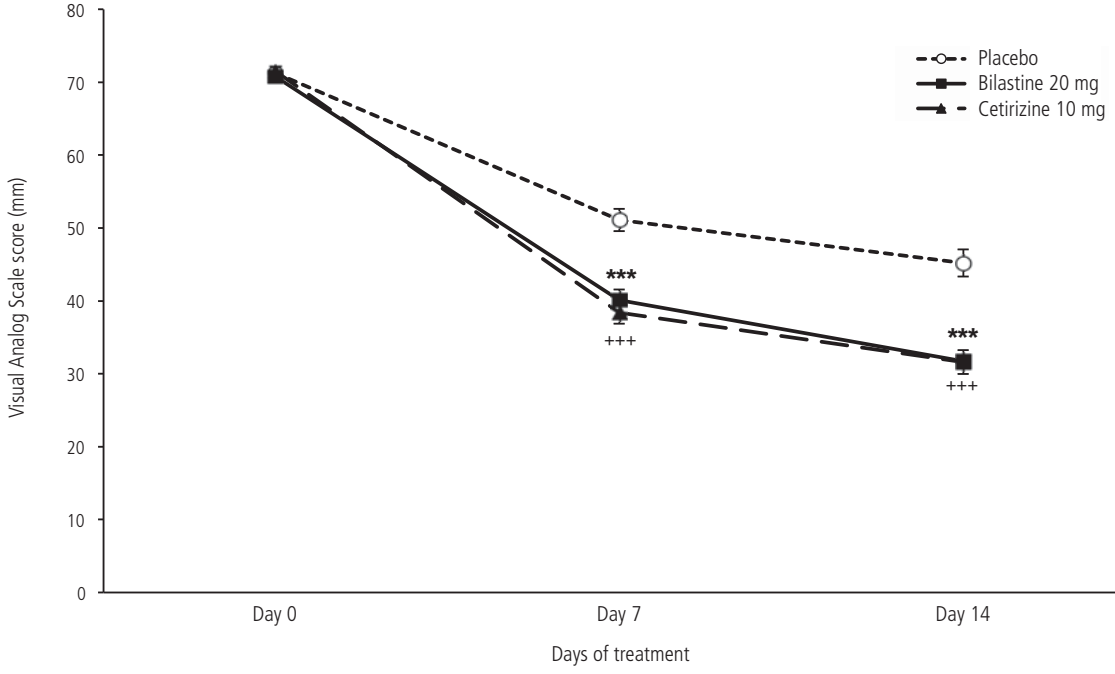

Figure 1. Global reduction in discomfort, assessed by the visual analog scale (mm), in patients with seasonal allergic rhinitis treated with placebo, bilastine 20 mg or cetirizine 10 mg.
*** p<0.001 (bilastine vs placebo)
+++ p<0.001 (cetirizine vs placebo).

Regarding the VAS scores, a clear improvement was noticed over the course of the treatment in the two active drug groups versus placebo, with an almost identical profile in both cases (40% on day 7 and 49% on day 14 of treatment).

In another study, comparing bilastine 20 mg/day versus cetirizine 10 mg/day and placebo in 681 patients randomized to three homogeneous groups over a period of 14 days [33], a significant reduction was again observed in the symptom scores in both active drug groups versus placebo ($p<0.001$) – with no significant differences in the efficacy profiles between bilastine and cetirizine. In this study the variable HRQoL was not evaluated as such, though a global reduction was observed in discomfort assessed by VAS over the course of the study that proved to be identical in the two active drug groups (54.6%), and with significant differences versus placebo (35.5%, ANOVA $p<0.001$)(Figure 1).

Changes in HRQoL in the cumulative data analyses in allergic rhinitis

Finally, considering the cumulative data for bilastine in which HRQoL was determined with the RQLQ [36], a significant improvement was observed in the global RQLQ score with bilastine 20 mg versus placebo, affecting both the overall scores and the scores of the different RQLQ domains separately considered (Table 4). It can therefore be concluded that the antihistamine bilastine contributes to improve the HRQoL in patients with allergic rhinitis, at least in the context of the clinical trials.

Bilastine and HRQoL in Chronic Urticaria

Urticaria and angioedema are also common causes of consultation in dermatology, allergology and emergency care. A population-based study performed in Spain estimated a cumulative incidence of acute urticaria of 18.72%, versus 0.65% in the case of CU, in general population [37]. Non-sedative antihistamines are regarded as the first choice symptomatic treatment, with a scientific level of evidence 1 and a degree of recommendation A [38,39]. In comparative trials of antihistamines for the treatment of CU, no significant differences are generally observed in symptom control or in the HRQoL parameters among the different drug substances [40]

As mentioned at the begining, we must consider whether this concept of HRQoL is interchangeable between respiratory allergy and CU, and whether we can expect the same from a given antihistamine in one or in the other disease. Comparisons between patients with CU and patients with respiratory allergic disease (assessed by generic questionnaires such as the SF-36 and SAT-P) indicate that patients with CU are more affected in their daily life than patients with rhinitis and/or asthma, in relation to aspects such as sleep, eating behaviour, occupational activity and general physical and psychological functioning [3]. This important degree of affectation persists when we try to establish comparisons on HRQoL between patients with CU and other skin diseases. When the mentioned DLQI is used [15], CU is seen to worsen HRQoL to an extent similar to atopic dermatitis, with a greater impact than other skin conditions such as psoriasis, acne, vitiligo or Behçet's disease [8]. Another skin disease-specific questionnaire, the Skindex-29, records higher scores (poorer HRQoL) in CU, determined by the coexistence of psychiatric processes (anxiety, depression or somatized disorders) [41] and, when generic questionnaires are used to compare it with other diseases, CU has demonstrated subjective limitations at least similar to those of severe ischemic heart disease pending aortocoronary surgery [42]. Wheals and angioedema affect the patients physical appearance, and CU is associated with pain, discomfort and interference with sleep [43] – a situation which may lead to reductions up to 30% in work/school performance as assessed with instruments such as the DQLI or the *Work Productivity and Activity Impairment* (WPAI) tool [44].

Different skin disease-specific questionnaires have been applied to CU, although as said, the most widely used instrument in most clinical trials is the DLQI [15], which contains 10 questions in 6 domains (symptoms and feelings, daily activities, leisure, work / school, personal relations and treatment). In general, answers are scored from 0-3 (0 = "*does not affect me at all*", and 3 = "*affects me very much*"); the DLQI score is calculated adding the score for each question, with a

Tabla 4. Bilastine and HRQoL in allergic rhinitis: cumulative data. Change in HRQoL score at the end of the study (day 14 or 28) versus baseline score. Results expressed as the mean (SD).

RQLQ domains	Placebo n=622	Bilastine 20 mg n=605	Bilastine 40 mg n=239	Cetirizine 10 mg n=432	Desloratadine 5 mg n=185
Activity	-1.73 (1.56)	-1.98 (1.60)**	-2.15 (1.57)***	-1.99 (1.67)**	-1.87 (1.59)
Sleep	-1.47 (1.76)	-1.50 (1.64)	-1.77 (1.83)*°	-1.64 (1.84)	-1.29 (1.63)
Non-nose/non-eye symptoms	-1.33 (1.46)	-1.47 (1.41)*	-1.65 (1.52)**	-1.52 (1.49)	-1.32 (1.27)
Practical problems	-1.94 (1.84)	-2.17 (1.79)*	-2.41 (1.78)***	-2.36 (1.92)***	-2.13 (1.81)
Nasal symptoms	-1.77 (1.63)	-1.93 (1.64)*	-2.11 (1.59)**	-2.08 (1.70)**	-1.94 (1.55)
Eye symptoms	-1.31 (1.51)	-1.56 (1.60)**	-1.56 (1.60)**	-1.52 (1.55)**	-1.62 (1.43)
Emotions	-1.38 (1.49)	-1.53 (1.55)	-1.74 (1.5)**	-1.65 (1.76)	-1.19 (1.26)
Total	-1.56 (1.32)	-1.74 (1.31)*	-1.92 (1.34)**	-1.82 (1.43)**	-1.63 (1.16)

*, **, ***p-value <0.05, <0.01, <0.001 drug vs placebo
°= p<0.05 vs. bilastine 20 mg

Table 5. Bilastine and HRQoL, according to the DQLI in chronic urticaria. Change in HRQoL score at the end of the study (day 28) versus baseline score. Results expressed as mean improvement (SD) from day 0 to day 28 of treatment

Variable [mean(sd)]	Bilastine 20 mg n=172	Levocetirizine 5 mg n=163	Placebo n=181	ANOVA
HRQoL with DQLI (global)	-9.45 (6.98)***	-8.94 (6.53)***	-5.93 (7.67)	p<0.001
Symptoms and feelings	-2.68 (1.87)***	-2.67 (1.86)***	-1.64 (2.04)	p<0.001
Daily activities	-1.98 (1.7)**	-1.84 (1.7)*	-1.29 (1.85)	p<0.001
Leisure	-1.62 (1.6)**	-1.43 (1.46)	-1.01 (1.76)	p=0.002
Work/study	-1.16 (1.37)	-1.35 (1.3)**	-0.86 (1.4)	p=0.008
Personal relations	-1.52 (1.89)**	-1.29 (1.38)	-0.92 (1.71)	p=0,005
Treatment	-0.48 (0.91)*	-0.36 (0.73)	-0.23 (0.73)	p=0.018

*, **, ***p value <0.05, <0.01, <0.001 drug vs placebo

maximum score of 30 and a minimum score of 0: higher scores imply poorer HRQoL. The DLQI has been shown to be useful in assessing the most prevalent chronic skin disorders, and as stated previously, it has also been specifically validated for its application to CU [16].

The efficacy of bilastine in relation to HRQoL in CU has been evaluated versus levocetirizine. In this sense, bilastine was found to be more effective than placebo and at least as effective as the comparator drug for the control of itching and in terms of reducing the number and size of the wheals. This trial versus levocetirizine was carried out in a total of 525 patients, and HRQoL was assessed with the DLQI. Improvement was observed in the global DLQI score, as well as in all of its individual domains (p<0.001), with no differences between the two active drug groups (Table 5). General discomfort as assessed with the VAS showed a similar behaviour [45]. It can therefore be concluded that the antihistamine bilastine contributes to improve the HRQoL in patients with chronic urticaria, at least in the context of the analyzed clinical trial.

Conclusion

The evaluation of quality of life (QoL) and its modification through therapeutic interventions has become a priority concern in recent years and a requirement on the part of the regulatory agencies for clinical trials with new drugs – particularly in relation to allergic rhinitis and urticaria. In these diseases a number of generic questionnaires have been used, such as the SF-36, and particularly specific instruments such as the RQLQ (applied to allergic rhinitis) or the skin disease-specific DLQI.

In the course of its clinical development, bilastine in a single daily dose of 20 mg has been shown to be more effective than placebo and as effective as cetirizine, fexofenadine and desloratadine in controlling the symptoms of seasonal allergic rhinitis. HRQoL, based on the RQLQ, has been evaluated as a secondary objective in three clinical trials of allergic rhinitis, involving a total of 2335 patients. The improvement in HRQoL in these studies was in all cases proportional to the symptom improvement. Likewise, HRQoL has been studied with the DLQI in the most important clinical trial carried out in CU, versus levocetirizine and placebo, in a total of 525 patients – with improvement in all the DLQI domains for both active drug groups, in parallel to the decrease in itching and in the number and size of the wheals.

In general, the data obtained relating to changes in HRQoL with these specific questionnaires are concordant with the mean global VAS scores and their changes between the begining and the end of the treatment period for all the trials carried out with bilastine and all its comparators in those studies where the VAS was used as a single index or as a complement to the measurements of HRQoL.

It can therefore be concluded that the antihistamine bilastine, in the context of the clinical trials performed, contributes to improve the HRQoL in patients with both allergic rhinitis and CU. Provided these data can be extrapolated to patients in the real life setting, in the near future we will have a drug of undoubted interest among the non-sedative H1 antihistamines that do not interact with the P450 cytochrome system.

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Conflicts of interest

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Pharmaceuticals, FAES; Joaquín Sastre Domínguez with: GSK, Novartis, Stallergenes, UCB, MSD, ALK-Abelló, Stallergenes, FAES; Antonio Luis Valero Santiago with: MSD, Uriach, Dr. Esteve, Chiesi, GSK, FAES, UCB, Stallergenes.

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